REMARKS

As an initial matter, Applicants note that the PTO-1449 forms attached to the outstanding Office Action are not initialed by the Examiner. Thus it is not clear if the USPTO has had the chance to consider the cited references fully. The Examiner is respectfully requested to send the undersigned initialed copies of the PTO-1449 forms indicating that the references have been considered. If copies of any of the references are required, the undersigned will be happy to send them to the Examiner promptly on request.

Claims 51-60 are pending. Claim 51 is amended herein. Support for the amendment can be found throughout the instant application including the claims and Drawings as filed originally.

Claim 60 is newly added. Particular support can be found at pg. 26, line 5 to pg. 27, line 16 (disclosing multivalent MHC complexes generally). See also pg. 26, lines 5-13 in which multivalent MHC fusion complexes are generally taught.

Referring to page 2 of the Action, Applicants have amended the application to reflect the correct priority information.

Claims 51-59 stand rejected under 35 USC §112, second paragraph, as being indefinite on various grounds. Applicants respectfully disagree in part.

The Office has taken the position that it is unclear from the claims whether Applicant intended to claim a composition in which linked MHC domains are derived from different alleles or the same molecule. Action at pg. 2. Respectfully, the claims are abundantly clear as written, especially in view of Applicants' specification and knowledge of MHC molecules in this field.

In particular, one working in this field reading Applicants' specification would understand that the claimed compositions can be made and used with linked MHC domains that can be the same or different. For instance, pg. 26 describes how activation of particular hybridomas requires multivalent MHC molecules. One working in the field would appreciate and understand the more general concept that multivalency is not tied to any particular MHC allele. Moreover, pg. 27 of the Application discloses manipulations that can be practiced regardless of whether or not MHC domains are the same or different. The claims particularly point out and distinctly claim these embodiments.

Claims 51-59 stand further rejected under 35 USC §112, second paragraph, on grounds that it is unclear as to whether each MHC molecule in the complex presents an identical or different peptide. Applicants disagree that there is an ambiguity in the claims as written. A worker reading Applicants specification would fully understand that the multivalency of the claimed composition is not tied to any particular peptide sequence or binding groove. The claims particularly point out and distinctly claim embodiments in which these claim features are the same or different.

Accordingly, claims 51-59 would not be seen as indefinite by one working in this field. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim 51 was viewed as unclear by the USPTO for reciting "increasing or decreasing T cell ....development". While Applicants respectfully disagree with the position taken, basis for it has been addressed by this submission. See amended claim 51 (reciting activity instead of development).

Claims 51 and 54 stand rejected under 35 USC 103 as being unpatentable over Clark et al. (US Pat. No. 5,260,422; "Clark") in view of McCluskey et al. (*J. Immunol.* (1988) 141: 1451; "McCluskey"). Applicants respectfully traverse.

As understood, the position was taken that Clark reports that the peptide and MHC Class II molecule can be covalently linked or that the peptide and MHC molecule may be linked via peptide linkers. The position was further taken that Clark reports that an MHC Class II molecule may be terminally truncated to delete transmembrane and cytoplasmic domains. It is also stated in the Office Action that the Clark reference reports a presenting peptide may be attached to the N-terminal end of the MHC Class II molecule. Applicants cannot agree as follows:

Clark simply fails to teach or suggest Applicants' claimed invention either taken by itself or in combination with McCluskey et al. as relied on.

For example, **Clark provides no suggestion of a linker interposed between a presenting peptide and MHC molecule** as Applicants claim.

On this basis alone, the rejection fails to withstand scrutiny.

At page 3 of the Office Action, it is stated that "The [Clark] Patent also discloses * * * that the peptide and the MHC molecule may be linked via peptide linkers (see Column 13, 45-47, in particular)."

In contrast to the Office position, the cited disclosure from Clark clearly does not suggest an interposed linker sequence as found in claim 51. Rather, Clark merely reports that the MHC molecule and autoimmune antigen peptide and the MHC component may be joined via a peptide bond. A peptide bond is not a linker. Thus, Clark discloses the following at column 13, lines 45-51:

> As demonstrated above, the autoimmune antigen peptide and the MHC component may be linked via **peptide linkages**. However, other modes of linkage are obvious to those of skill in the art, and could include, for example, attachment via carbohydrate groups on the glycoproteins, including, e.g., the carbohydrate moieties of the alpha-and/or beta-chains.

In support, Clark is understood to report certain molecules that have non-covalently bound antigenic peptides. All of the examples of Clark describe a MHC molecule with a non-covalently associated antigenic peptide. Moreover, Clark's proposed method of forming a covalently bound system -- photo affinity labeling (see Clark et al. at column 12, lines 52-54) -- is well recognized as a relatively nonspecific method. That method would not be not suitable for attaching an antigenic peptide in which the peptide could function effectively and modulate T cell activity in accordance with Applicants' invention. In other words, such a nonspecific procedure as photo affinity labeling would not be expected to position an antigenic peptide whereby the peptide could function effectively and modulate T cell activity.

Indeed, **Clark provides absolutely no description of a covalently bound antigenic peptide** that was actually produced. **Clark provides no or insufficient information about where such a peptide could be positioned** so as to make an MHC molecule that could be used to make a multivalent MHC fusion complex.

On this further basis, there is no grounds for maintaining the present obviousness rejection.

In further support of Applicants' position, it is requested that the attached Rule 132 Declaration ("Declaration") of Dr. Peter Rhode be considered.

According to ¶ 3 of the Declaration, Dr. Rhode found that having a linker sequence as provided by his patent application was important for activity of the MHC complex and larger multivalent complex. That information is disclosed in the instant application eg., at pg .13, line 1 to pg. 14, line 28. As stated by Dr. Rhode, the multivalent MHC fusion complexes of his application are not disclosed or rendered obvious by the Clark patent nor does it provide for a linker sequence interposed between the MHC molecule and a presenting peptide. Decl. at ¶ 7.

None of the other cited references remedy this deficiency of the Clark reference.

Dr. Rhode also found that adding a leader sequence to the multivalent MHC fusion complexes assisted the construction and function of the molecules. Decl. at ¶¶ 4 and 6. As observed by Dr. Rhode at ¶ 6 of the Declaration, Clark taught away from the claimed invention by advocating that leader sequences not be used. None of the cited McCluskey, Selick or Tomalia references remedy this defect or provide for the benefits of adding a leader sequence to the claimed multivalent MHC fusion complexes as found by Dr. Rhode.

The multivalent MHC fusion complex of claim 51 features a leader sequence attached to the presenting peptide of the MHC class II molecule. Such a leader sequence provides advantages that are disclosed throughout the instant application. See eg., pg. 17, line 7 to pg. 18, line 7 (disclosing benefits in expression, positioning of the presenting peptide, and translation).

As cited, neither Clark or McCluskey teaches or suggests these benefits particularly with respect to a multivalent MHC fusion complex or MHC components thereof.

Moreover, no suggestion would have existed to modify molecules described by Clark et al. to be multivalent as proposed by the Office Action. Clark et al. (filed as a continuation-in-part application after the publication of McCluskey) reports use of only monovalent molecules.

As Dr. Rhode states at ¶¶ 8-10 of the Declaration, the procedure disclosed in Clark would not be expected to make a functional MHC molecule. Such a molecule could not be used effectively to make the claimed multivalent MHC fusion complexes.

In particular, Dr. Rhode stated that Clark reports **directly** linking a specific AchR sequence to the N-terminus of MHC molecules. Decl. at ¶ 8. According to Dr. Rhode, the patent provides no suggestion or teaching to position an autoimmune peptide (attached by the linker to the MHC molecule) in the MHC binding groove. Decl. at ¶¶ 8-9. Such a complex in which peptide is directly linked to an MHC molecule could not be used to make the presently claimed

multivalent MHC fusion complexes.

Indeed, and as stated by Dr. Rhode at ¶ 11, Clark et al. describes a specific linked peptide (AChR) that could not effectively bridge the length between the peptide and MHC molecule of the claims.

As also stated by Dr. Rhode at ¶ 12 of the Declaration, a worker following the procedure outlined in the Clark patent would not produce an MHC molecule having a functional MHC peptide. Such a molecule could not be used to make the claimed multivalent MHC fusion complexes.

As cited, none of McCluskey or Clark remedies these shortcomings. Accordingly, there is no basis for the instant obviousness rejection. Reconsideration and withdrawal thereof are respectfully requested.

Applicants respectfully disagrees with the rejection on further grounds.

As cited, McCluskey et al teaches that MHC class I fusion complexes can be made multivalent. However, the class I fusion complexes from McCluskey et al. are quite different from the MHC class II molecules of Applicants' multivalent MHC fusion complexes.

For instance, there are substantial differences between MHC class I and class II molecules. A worker reading Applicants' specification would appreciate that the magnitude of these differences are large and that what is reported to work for one type of immune system molecule (class I) would necessarily work for completely different molecules.

The chimeric molecules provided by McCluskey as relied on are substantially different to those claimed by Applicant. There is simply nothing in McCluskey or Clark that teaches, suggests or provides any motivation to substitute McCluskey's molecules for those of the

invention.

In particular, and as Dr. Rhode points out in the Declaration, the chimeric molecules of McCluskey are quite different from those claimed. Decl. at ¶¶ 13-21.

That is, McCluskey provides MHC **class I** molecules that are structurally and functionally different from the MHC **class II** molecules of the invention. Decl. at ¶¶ 13-14. Specifically, the MHC class II molecules include α and β chains. In marked contrast, the MHC class I molecules reported by McCluskey have class I α and $\beta 2$ microglobulin chains. The α and β chains of the MHC class II molecule cooperate to bind antigen. In marked contrast, the MHC class I molecule uses its single and different α chain to bind antigen. Decl. at ¶¶ 13-15.

The structural and functional differences between MHC class I and MHC class II molecules are real and substantial. Decl. at ¶¶ 11-15. There is simply nothing in the cited references taken alone or in combination with each other that provides any specific teaching or suggestion that one could make the claimed multivalent MHC fusion molecules simply because McCluskey reported some success doing so with completely different immune system molecules.

Clark as cited does not remedy the shortcomings apparent from the McCluskey et al article as cited.

Applicants respectfully disagree with the rejection on additional grounds.

In particular, there are other significant differences between the chimeric molecules disclosed by McCluskey and the claimed MHC class II molecules of the invention. Decl. at ¶¶ 16-21.

For instance, McCluskey's molecules are reported to be a composite of MHC class I and

non-classical MHC domains. These are quite unlike the claimed MHC class II molecules. Decl. at ¶16. There is no specific teaching or suggestion in McCluskey taken alone or in combination with the other cited references to include them in MHC class II molecules.

Specifically, McCluskey's molecules have different domain and glycosylation structures (Decl. at ¶¶ 17, 20), alloreactive elements (Decl. at ¶ 18), and folding potential (Decl. at ¶ 19) when compared to the claimed MHC class II molecules. McCluskey's chimeric molecules work without presenting peptide antigen. Decl. at ¶ 18. In contrast, the claimed MHC class II molecules require an appropriately folded presenting peptide to work. Decl. at ¶19.

There is nothing in McCluskey that teaches or suggests that given the substantial structural and functional differences between McCluskey's chimeric molecules and MHC class II molecules, that it would be obvious to use methods disclosed in the reference to make the claimed MHC class II molecules.

As cited, nothing in the Clark, McCluskey, Selick or Tomalia references (taken individually or together) remedy these defects.

In view thereof, there is no basis for the instant §103 rejection. No *prima facie* case has been made. Reconsideration and withdrawal are respectfully requested.

Claims 52 and 53 stand rejected as obvious under 35 USC §103 as being unpatentable over Clark in view of McCluskey and further in view of WO 93/10220 to Selick et al. Applicants respectfully traverse.

The deficiencies of Clark and McCluskey as relied have already been pointed out. Selick discloses an MHC component linked to an immunoglobin constant region component. As cited, it does not remedy the shortcomings of Clark and McCluskey as discussed above.

Accordingly, there is no basis for the obviousness rejection as currently formulated. Reconsideration and withdrawal therefore are requested.

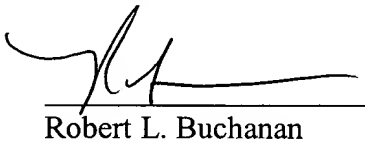
Claims 55-59 stand rejected as being unpatentable over Clark in view of McCluskey and further in view of the Tomalia patent (U.S Pat. No. 5,338,532; "Tomalia"). Applicants respectfully traverse.

The deficiencies of Clark and McCluskey as relied have already been pointed out. Tomalia teaches certain starburst conjugates. As relied on by the Office, it does not remedy the shortcomings of Clark and McCluskey as discussed above.

Accordingly, there is no basis for the obviousness rejection as currently formulated. Reconsideration and withdrawal therefore are requested.

Applicants submit that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicants' attorney would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

Respectfully submitted,



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